CEREBRO-HEPATO-RENAL (ZELLWEGER) SYNDROME

Selective neuronal lipidosis and neuroaxonal dystrophy of the dorsal nucleus of Clarke and lateral cuneate nucleus were the neuropathological findings in 3 males with Zellweger syndrome examined at the Medical Unit S Carolina, Charleston, SC, the John F. Kennedy Institute, Johns Hopkins Univ, Baltimore, MD, and the Philadelphia Children's Hosp. Large amounts of abnormal cholesterol esters containing saturated and monosaturated very long-chain fatty acids were demonstrated in the striated neurons of the dorsal thoracic cord. The CNS neurons of these patients manifested the same morphological alteration as adrenocortical cells of adreno-leukodystrophy, and many of the striated neurons were degenerate or necrotic. It is suggested that a more generalized defect in neuronal fatty acid metabolism may explain the neuronal migration defects characteristic of Zellweger syndrome. These consist of pachygyria, micropolygyria and cerebral and cerebellar heterotopia. (Powers JM et al. Neuronal lipidosis and neuroaxonal dystrophy in cerebro-hepato-renal (Zellweger) syndrome. Acta Neuropathol (Berl) 1987:73:333-343).

COMMENT. CHR (Zellweger) syndrome, transmitted as an autosomal recessive, is invariably fatal within a few months after birth. Prenatal diagnosis may be made by amniocentesis and the production of very-long-chain fatty acids (VLCFA) from cultured amniocytes (Lancet 1984:1:1234. Mosher AE et al. N Engl J Med 1984:310:1141). The determination of VLCFA in the blood permits prompt diagnostic confirmation of CHRS in the infant with dysmorphic facial and skull features, liver enlargement and fibrosis, renal cysts, stippled calcifications of the patellae, Brushfield's spots, optic atrophy and retinal pigmentation. Zellweger syndrome is a peroxisomal disorder. The lacking peroxisomes are cytoplasmic organelles containing oxidases and catalase and are involved in metabolism of hydrogen peroxide, fatty acids and bile acids.

SEIZURE DISORDERS

DIAZEPAM SENSITIVITY AND INTRACTABLE SEIZURES

The benzodiazepine sensitivity test, an intravenous bolus of diazepam (0.2 mg/kg) under EEG control, was used in 40 children with intractable seizure disorders treated in the Paediatric Neurology Service and the Dept Neurology and Clinical Neurophysiology, Royal Hospital for Sick Children, Edinburgh. The etiology and clinical patterns of seizures were heterogeneous, 50% symptomatic of various causes and 63% with a mixed seizure disorder, atypical absences, myoclonic and drop or atonic seizures predominating. EEG abnormalities were severe and persistent. Many different drugs had been used but 29 (73%) patients had not received benzodiazepines.

A positive effect, defined as abolition of abnormal EEG activity often with appearance of fast activity, was obtained in 53% of the total group. The response was negative in 6 of 7 patients in non-convulsive status and in 7 of 9 patients with Lennox Gastaut syndrome, 2 showing exacerbations of EEG paroxysms and clinical seizures. All 5 with focal spikes responded whereas only 3 of 6 with hypsarrhythmia showed improvement in the EEG.

Of 32 patients treated subsequently with long-term oral benzodiazepines, 21 (66%) showed improvement in seizure control. Among

those benefitted, the diazepam sensitivity test had been positive in 76%. Of 11 patients unresponsive to oral benzodiazepines, only 36% had shown a positive sensitivity test. The authors conclude that the test is of value in long-term management of intractable childhood seizures but emphasize the variability and unpredictability of the response to oral benzodiazepines. (Livingston JH et al. Benzodiazepine sensitivity testing in the management of intractable seizure disorders in childhood. Electroencephalography and Clin Neurophysiol 1987:67:197-203).

COMMENT. This practical study confirms the value of the EEG and intraveneous drug sensitivity in the management of childhood epilepsy but with some limitations. It contradicts the recommended choice of benzodiazepines in the treatment of non-convulsive status (Gastaut H. Adv Neurol 1983:34:15-36. Editorial, Lancet 1987:1:958). Development of tolerance is the greatest limitation to the long-term use of benzodiazepines in myoclonic and other epilepsies, occurring in 80% of 36 children treated with nitrazepam at Children's Memorial Hosp, Chicago (Millichap JG, Ortiz W. Amer J Dis Child 1966:112:242).

VIGABATRIN IN DRUG-RESISTANT EPILEPSY

A double-blind, placebo-controlled, crossover study of oral Vigabatrin (2-3 g/d) as add-on therapy for 31 patients with drug-resistant seizures is reported from the Neurological Clinic, Univ of Bologna School of Med, Italy. Both children and adults were included. Those with complex partial seizures and temporal spikes responded whereas patients with mixed seizure types and multi-focal EEG abnormalities were not benefitted. Drowsiness was the most frequent side-effect and concomitant phenytoin serum concentrations fell during Vigabatrin treatment. (Tassinari CA et al. Double-blind study of Vigabatrin in the treatment of drug-resistant epilepsy. Arch Neurol 1987:44:907-910).

COMMENT. Vigabatrin (γ-vinyl GABA) is an inhibitor of γ-aminobutyric acid (GABA)-transaminase. Increases in CNS-GABA concentrations in laboratory animals and CSF-GABA in patients treated with Vigabatrin have been associated with anticonvulsant activity. Several laboratory and clinical reports of this drug have appeared in the literature in the past decade, mostly with favorable results in patients with complex partial seizures (see Browne TR et al. Neurology 1987:37:184. Rimmer EM, Richens A. Lancet 1984:1:189).

The finding of microvacuoles in the white matter of the CNS of laboratory animals has not been duplicated in autopsy reports on patients who have died from causes independent of Vigabatrin therapy or in CT scans but has prompted the FDA to put a hold on clinical trials in the USA since 1983. At present, 31 adult patients with complex partial seizures are in the on-going collaborative study but no patient may be added (R. Miketta, M.D., Merrell Dow Pharmaceuticals, personal communication). Phase III trials are continuing in other countries and registration of the drug is expected in France in 1988. Side effects in adults treated with Vigabatrin for complex partial seizures have included drowsiness, ataxia, dizziness, headache and skin rash. Levels of SGPT have shown decreases, as might be expected, but no liver or blood disorders have been reported.